Previous Doc Next Doc Go to Doc#
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L3: Entry 1 of 1 File: USPT Mar 20, 2001

US-PAT-NO: 6203787
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TITLE: Treating tumors using implants comprising combinations of allogeneic cells

DATE-ISSUED: March 20, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
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US-CL-CURRENT: 424/93.3; 424/93.7, 424/93.71, 435/325, 435/347, 435/366, 435/372, 435/373, 435/383

CLAIMS:

What is claimed as the invention is:

1. A method for preparing a pharmaceutical composition containing alloactivated human donor lymphocytes for treating a tumor in a human patient, comprising the steps of:

a) coculturing the following cells ex vivo:

lymphocytes from a first human donor allogeneic to the patient, and leukocytes from a second human donor allogeneic to both the first human donor and the patient, so as to alloactivate the lymphocytes; and

b) harvesting the cocultured cells and preparing them for human administration at a time after initiation of the coculturing when the harvested cells, upon implantation in the bed of a solid tumor in the patient, are effective in treating the solid tumor or eliciting an anti-tumor immunological response in the patient.

2. The method according to claim 1, wherein the cocultured cells are harvested at a time when implantation of the cocultured cells elicits a response in the patient against the tumor.

3. The method according to claim 1, wherein the cocultured cells are harvested at a time when a single implantation of the cocultured cells in the bed of the solid tumor is effective in the treatment of the tumor.

4. The method according to claim 1, wherein the harvesting in step a) is performed at about the time that at least one of the following criteria is met:

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i) when the level of secretion of IFN-.gamma. by the cultured cells is highest; or

ii) at about 48 to 72 hours after initiation of the culture.

5. The method according to claim 1, wherein leukocytes from at least two different human donors allogeneic to both the first human donor and the patient are cocultured in step a).

6. The method according to claim 1, wherein the coculturing of step a) is conducted in a medium containing an H2 receptor antagonist.

7. The method according to claim 6, wherein the H2 receptor antagonist is cimetidine.

8. The method according to claim 7, wherein the cimetidine is present in the culture medium at a concentration between about 5 .mu.g/mL and about 100 .mu.g/mL.

9. A method for preparing a cultured cell population containing alloactivated human donor lymphocytes effective in treating a tumor in a human patient, comprising the steps of:

a) obtaining lymphocytes from a first human donor allogeneic to the patient, and

b) obtaining leukocytes from a second human donor allogeneic to both the first human donor and the patient;

c) coculturing the lymphocytes ex vivo with the leukocytes so as to alloactivate the lymphocytes;

d) harvesting the cocultured cells from culture at a time when the harvested cells, upon implantation in the bed of a solid tumor in the patient, are effective in treating the tumor or eliciting an anti-tumor immunological response;

e) washing culture medium from the harvested cells; and

f) verifying that the washed cells are sufficiently sterile for human administration.

10. The method according to claim 9, incorporating one or more of the following features:

i) obtaining at least about 2.times.10.sup.9 peripheral blood mononuclear cells from the first human donor in step a);

ii) obtaining at least about 2.times.10.sup.8 peripheral blood mononuclear cells from the second human donor in step b);

iii) blocking proliferation of the leukocytes prior to step c);

iv) coculturing the donor lymphocytes with the patient leukocytes at a ratio

of about 5:1 to 20:1 in step c); or

v) producing at least about 2.times.10.sup.9 cocultured cells suitable for human administration after completion of step f).

11. A pharmaceutical composition prepared according to the method of claim 1, which, upon implantation at or around the site of a solid tumor in said human patient with or without partial resection of the tumor, is effective in eliciting an anti-tumor immunological response.

12. A pharmaceutical composition prepared according to the method of claim 1, which, upon implantation at or around the site of a solid tumor in a human patient with or without partial resection of the tumor, is effective in the treatment of the tumor.

13. The pharmaceutical composition of claim 11 having one or more of the following features:

i) containing between about 2.times.10.sup.9 and 2.times.10.sup.10 cultured peripheral blood mononuclear cells originating from the first donor;

ii) containing between about 1.times.10.sup.8 and 2.times.10.sup.9 cultured peripheral blood mononuclear cells originating from the second donor;

iii) being substantially free of any exogenously added lymphocyte proliferation agent;

iv) containing a physiologically compatible carrier selected from the group consisting of physiological saline, buffered medium, and clotted plasma.

14. The pharmaceutical composition of claim 11, wherein a single implantation of the cocultured cells is effective in eliciting an anti-tumor immunological response.

15. A method of eliciting an anti-tumor immunological response in a human patient, comprising implanting in or around the bed of a solid tumor in the patient a pharmaceutical composition according to claim 10.

16. A method of treating a tumor in a human patient, comprising implanting in or around the bed of a solid tumor in the patient a pharmaceutical composition according to claim 12.

17. The method according to claim 14, further comprising the additional step of administering to the patient at a site distant from the tumor a second composition comprising alloactivated human lymphocytes allogeneic to the patient mixed with inactivated tumor cells from the patient or inactivated progeny of such tumor cells.

18. The method according to claim 15, wherein the tumor is a malignancy selected from the group consisting of melanoma, pancreatic cancer, liver cancer, colon cancer, prostate cancer, and breast cancer.

Previous Doc Next Doc Go to Doc#

L6: Entry 1 of 2 File: USPT Mar 27, 2001

US-PAT-NO: 6207147
DOCUMENT-IDENTIFIER: US 6207147 B1

TITLE: Cancer immunotherapy using tumor cells combined with mixed lymphocytes

DATE-ISSUED: March 27, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
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Thompson; James A.	Aliso Viejo	CA		
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US-CL-CURRENT: 424/93.1; 424/93.3, 435/347, 435/363, 435/366, 435/372, 435/373, 435/374

CLAIMS:

What is claimed as the invention is:

1. An immunogenic composition suitable for administration to a human, comprising an effective combination of:

a) stimulated lymphocytes allogeneic to the human; and

b) tumor-associated antigen from the human;

wherein the combination is effective to elicit an immune response to the tumor-associated antigen in the human subject after administration.

2. The immunogenic composition of claim 1, wherein said tumor-associated antigen is comprised in a primary tumor cell from said human, or a progeny of such a tumor cell obtained by culturing the tumor cell ex vivo.

3. The immunogenic composition of claim 1, wherein said tumor-associated antigen is comprised in an extract of a primary tumor cell from said human, a progeny of a primary tumor cell from said human, or a combination thereof.

4. The immunogenic composition of claim 1, wherein said stimulated lymphocytes have been stimulated by culturing with leukocytes allogeneic to the lymphocytes.

5. The immunogenic composition of claim 1, where said stimulated lymphocytes have been stimulated by culturing with a recombinantly produced cytokine, a mitogen, or with a cell genetically altered to secrete a cytokine at an

elevated level.

6. An immunogenic composition suitable for administration to a humans, comprising an effective combination of:

a) lymphocytes allogeneic to the human;

b) leukocytes allogeneic to the lymphocytes; and

c) an inactivated tumor cell population, consisting essentially of primary tumor cells obtained from the human, or the progeny of such cells;

wherein the combination is effective to elicit an immune response to the tumor cell population in the human subject after administration.

7. The immunogenic composition of claim 6, wherein the leukocytes are autologous to the human.

8. The immunogenic composition of claim 6, wherein the leukocytes are allogeneic to the human.

9. The immunogenic composition of claim 6, comprising leukocytes from at least three different human donors.

10. The immunogenic composition of claim 6, wherein the inactivated tumor cell population are selected from the group consisting of melanoma, pancreatic cancer, liver cancer, colon cancer, prostate cancer, and breast cancer cells.

11. The immunogenic composition of claim 6, wherein the leukocytes are inactivated.

12. The immunogenic composition of claim 6, wherein said lymphocytes comprise a cell that has been genetically altered to express a cytokine at an elevated level.

13. The immunogenic composition of claim 6, wherein said leukocytes and said lymphocytes are cocultured for a duration and under conditions sufficient for allogeneic stimulation of the lymphocytes, prior to combination with said tumor cell population.

14. The immunogenic composition of claim 6, wherein said coculturing is for a duration and under conditions sufficient to stimulate elevated cytokine secretion by the lymphocytes.

15. A unit dose of the immunogenic composition according to claim 6, wherein the number of said lymphocytes allogeneic to the leukocytes in the dose is between about 1.times.10.sup.8 and 2.times.10.sup.9.

16. A unit dose of the immunogenic composition according to claim 6, wherein the inactivated tumor cell population in the dose consists of between about 1.times.10.sup.6 and 5.times.10.sup.7 cells.

17. A method for producing the immunogenic composition of claim 1, comprising mixing:

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a) stimulated lymphocytes allogeneic to said human; with

b) tumor-associated antigen from the human.

18. A method for producing the immunogenic composition of claim 1, comprising mixing:

a) cells obtained from a coculture of lymphocytes allogeneic to said human and leukocytes allogeneic to the lymphocytes; with

b) primary tumor cells from the human, or progeny thereof.

19. A kit for producing the immunogenic composition of claim 1, comprising in separate containers:

a) stimulated lymphocytes allogeneic to the human; and

b) tumor-associated antigen from the human.

20. A kit for producing the immunogenic composition of claim 1, comprising in separate containers:

a) cells obtained from a coculture of lymphocytes allogeneic to said human and leukocytes allogeneic to the lymphocytes; and

b) primary tumor cells from the human, or progeny thereof.

21. A method for inducing an anti-tumor immunological response in a human, comprising administering an immunogenic amount of the immunogenic composition of claim 1 to the human.

22. A method for inducing an anti-tumor immunological response in a human, comprising administering an immunogenic amount of the immunogenic composition of claim 6 to the human.

23. A method for stimulating an anti-tumor immunological response in a human, comprising the steps of:

a) mixing ex vivo a first cell population comprising tumor cells, and a second cell population comprising lymphocytes allogeneic to the human, to produce a cell mixture; and

b) administering an immunogenic amount of the cell mixture to the human.

24. The method of claim 23, wherein said tumor cells comprises cells selected from the group consisting of melanoma, pancreatic cancer, liver cancer, colon cancer, prostate cancer, and breast cancer.

25. The method of claim 23, wherein said second cell population further comprises leukocytes allogeneic to the lymphocytes.

26. The method according to claim 23, wherein the second cell population contains leukocytes from at least three different human donors.

27. The method of claim 23, wherein the leukocytes are autologous to the human.

28. The method of claim 23, wherein the leukocytes are allogeneic to the human.

29. The method of claim 23, wherein said immunological response is a primary response.

30. The method of claim 23, wherein said immunological response is a secondary response.

31. The method of claim 23, wherein said human has been previously treated by administration of alloactivated allogeneic lymphocytes into a solid tumor in the human or at or around a site where a solid tumor or a portion thereof has been removed.

32. A method for treating a neoplastic disease in a human, comprising administering an effective amount of the immunogenic composition of claim 6 to the human.

33. A method for treating a neoplastic disease in a human, comprising the steps of:

a) mixing ex vivo a first cell population comprising tumor cells, and a second cell population comprising lymphocytes allogeneic to the human, to produce a cell mixture; and

b) administering an effective amount of the cell mixture to the human.

34. The method of claim 33, wherein said second cell population further comprises leukocytes allogeneic to the lymphocytes.

Previous Doc Next Doc Go to Doc#

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1: Biotherapy. 1994;8(1):41-50. Related Articles,

Use of human leukocyte antigen-mismatched allogeneic lymphokine-activated killer cells and interleukin-2 in the adopti immunotherapy of patients with malignancies.

Kimoto Y, Tanaka T, Tanji Y, Fujiwara A, Taguchi T.

Department of Oncology, Osaka University Medical School, Japan.

Clinical effects and side effects were studied in the adoptive immunotherapy patients bearing malignant diseases using human leukocyte antigen (HLA)-mismatched allogeneic lymphokine-activated killer (LAK) cells. Allogeneic LAK cells were induced from peripheral blood lymphocytes (PBL) of norma donors by means of initial stimulation with pokeweed mitogen (PWM). Six c patients applied in the adoptive immunotherapy showed clinical effects such partial or complete regression of pulmonary metastasis, pleural effusion and primary tumor. All pulmonary metastatic lesions were eliminated in one case this adoptive immunotherapy combined with chemotherapy. Generally toxic effects were chillness, fever and general fatigue which were reversible, and n allergic side effects occurred even though allogeneic LAK cells were injectec frequently except one patient who showed preshock like symptom accompan with leukocytopenia and continuous hypotension immediately after infusion was finally rescued. In the patients who received more than 10(11) of alloger LAK cells, anti-HLA class I antibodies appeared without any evidence of autoantibody. However, immunological side effects were never experienced after injection of allogeneic LAK cells even when the anti-HLA class I antibodies appeared in the patients. Taken together, allogeneic LAK cells cou be considered as alternative therapy for patients with malignancies who coul not supply sufficient materials of autologous LAK cells.

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PMID: 7547080 [PubMed - indexed for MEDLINE]

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